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行政院衛生署疾病管制局九十年度委託研究計畫

全民B型肝炎預防注射後兒童B型肝炎標記之五年縱向追蹤

（計畫名稱）

委 託 研 究 成 果 報 告

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計畫書中英文摘要素 (或成果摘要) _____ (Abstract)

請將計畫書之中英文摘要影印黏貼於此 ↓ 原計畫編號：DOH89-DC1023

關鍵字：B 型肝炎病毒、B 型肝炎表面抗原、B 型肝炎表面抗體、B 型肝炎核心抗

[研究目的]

(1) 爲瞭解全民 B 型肝炎在嬰兒期預防注射之長程免疫反應

(2) 爲探討學童無保護性抗體者，其對追加疫苗者之長程反應

[方法]：

我們以社區外表健康，在台灣施行全民 B 肝疫苗後出生之學童爲流行病學研究對象，對 1337 名 7 歲之一年級學童作 B 肝標記之長程追蹤。對於其中在一年級時檢查無保護性抗體者共 565 名，去除 9 名帶原者，我們予以建議施打一劑追加性 B 肝疫苗，共有 210 名學童接受此建議。另有 302 名學童雖未接受追加疫苗，但同意追蹤。本研究報告乃探討其二，三，四年級時之 B 肝病毒血清學反應，並比較已追加及未追加者之反應。

[結果]

在 7 歲時，表面抗體陽性率爲 78.1%，共 772 名(57.7%)學童具保護性 B 肝表面抗體，另有 9 名(0.7%)爲表面抗原陽性。其表面抗體在追蹤 3 年間年消失率爲 3.9%。其年自然抗體增強率在追蹤三年後爲 6.3%。表面抗體陽性率逐年下降。若將已追加疫苗者去除，則表面抗體陽性率(S/N>2.1)， 10 歲時降至 73.0%。三名新的 B 肝感染(anti-HBc 陽轉)者均發生在未接受加強注射者，已接受加強注射疫苗者並無人發生新感染，但此並未達統計學上有意義的差別。在追蹤期間並無新的 B 肝帶原者出現。原本不具保護性抗體者，因追加所獲得之抗體陰轉率較原來具保護性抗體者爲快速。

[結論]

全民嬰兒期 B 型肝炎預防注射對學童(11 歲以下)提供了充足的保護效益。此階段的學童雖然有三成以上兒童失去抗體，但並不需要給予加強的 B 肝疫苗。但我們應注意 anti-HBc 新陽轉的意義。

Summary

Objectives: (1) To study the long term follow-up of the immune response to universal hepatitis B vaccination in infancy, (2) To investigate the long effect of booster dose in school age children who had no protective antibody titers to hepatitis B surface antigen.

Methods: We conducted a community-based seroepidemiologic study of 1337 healthy 7 year-old children with long- term follow up in Taiwan one decade after the implementation of a mass hepatitis B vaccination program. A booster vaccination was suggested and accepted in 210 noncarrier children who did not have protective antibody titers to hepatitis B surface antigen at age 7. The hepatitis B markers were followed up yearly for 3 years to compare the serologic responses and infection rates between the boostered and nonboostered children.

Results: At 7 years of age, a total of 772 children (57.7%) had protective concentrations of surface antibody, and nine children (0.7%) were hepatitis B surface antigen (HBsAg) carriers. The annual disappearance rate of protective antibody to HBsAg (anti-HBs) was 3.9% when the children of positive protective levels of anti-HBs at 7 years of age were followed up for 3 years. The positive rates of anti-HBs decreased from 78.1% to 73.0% 3 years later when the boostered group was excluded. Although the "nonprotected" vaccinees showed immunologic memory to a booster dose, the new hepatitis B virus infection (anti-HBc seroconversion) occur all in the non-boostered children. Yet it does not reach statistically significant difference. The anti-HBs disappearance rate is faster in the initially "nonprotected" than those with protected antibody. No new carrier was noted during the 3 year follow-up.

Conclusions: According to these data, the universal hepatitis B vaccination program in

infancy provides adequate protection against hepatitis B virus infection for school age children (up to 10 years of age) and a booster vaccination was not recommended in these ages. But we have to pay attention to the significance of anti-HBc seroconversion.

Keyword : Hepatitis B Virus, HBsAg, anti-HBs, anti-HBc

Introduction

Most of the morbidity and mortality associated with HBV infection occurs many years later as the sequelae of chronic infection --- chronic hepatitis, liver cirrhosis, vascular disease, glomerulonephritis, and hepatocellular carcinoma.[1] Globally, about 5% to 10% of acutely infected patients will become chronic carriers of HBsAg, and about 25% of these persons will develop chronic cirrhosis of the liver and hepatocellular carcinoma.[2] In the endemic area such as Taiwan, as many as 15% to 20% of the general population are chronic HBV carriers[3], with hepatocellular carcinoma and liver cirrhosis being the leading causes of mortality.[4] Besides, the majority of chronic carriage of HBV results from infections that are contracted at an early age from their HBsAg carrier mothers.[5] Therefore, a universal vaccination program was launched in Taiwan in July, 1984 for newborn infants of HBsAg positive mothers. It was then extended to all newborns since July, 1986. Ten years later, universal HBV vaccination prevented 87% of HBsAg carriage and 85% of HBV infection (anti-HBc) in the children, by reducing both the perinatal and horizontal transmission.[6] By this way, the incidence of hepatocellular carcinoma in children has also declined.[7] It is proved to be a successful method to control HBV infection and its related disease.

The anti-HBs induced by hepatitis B vaccine does wane and may reach very low or even undetectable titers within a few years.[8] And HBV breakout is more frequently observed in low responders and particularly in those with a level of anti-HBs less than 10 mIU/mL.[9] In some long term follow-up studies of hepatitis B vaccination programs, instances of late infections and HBsAg carriage have been documented.[10,11] Therefore, booster vaccinations were suggested in later life by some authors.[10,11] On the other hand, the other authors objected the booster vaccinations since the number of memory B lymphocytes able to produce anti-HBs does not diminish as the level of antibody

declines[12] and anamnestic response to a single booster dose is documented.[13,14] Whether the booster doses prevent late infections and HBsAg carriage has been debated.[9,15]

We conducted a prospective follow-up study based on a cohort of randomly sampled, apparently normal school age children since 1994 in Taipei which is well representative of the general population. We report the seroprevalence of anti-HBs and the anti-HBs disappearance rate and natural booster rate are calculated. Among the children without protective anti-HBs, we compare the difference of seroconversion rate of anti-HBc and newly development of HBsAg carriage between boostered and non-boostered group. The results from the long-term follow up of community-based population may provide useful information for the strategy of booster vaccination program.

Methods

Subjects: Between March and May, 1994, 1337 apparently healthy children (693 boys and 644 girls) at 7 years of age from 3 major primary schools in 3 districts of Taipei (Zhong Zheng, Da An and Sin Yi Districts) were enrolled in this community-based study. All subjects were in the same grade. The participation rate was 77% and similar in the 3 schools (75, 77 and 79%, respectively). Parents of all enrolled children were requested to sign an informed consent form and to provide vaccination histories based on their immunization records. Among the 1337 children, 1199 subjects (89.7%) received three or more doses of HB vaccine during infancy. Primary vaccination conditions were similar in the three schools (89.6, 90.3, and 89.5% coverage rate, respectively).

According to the standard cited by the U.S. Advisory Committee on Immunization Practices (ACIP) and the World Health Organization (WHO), development of anti-HBs at a level of 10mIU/mL is widely viewed as making a protective response to hepatitis B vaccine.[16,17] The anti-HBs level was defined as low concentration if the radioimmunoassay count ratio of sample to negative control (S/N) was below 10, which was comparable with the protective titer of 10mIU/mL. A booster dose of HB vaccine was suggested for all the non-carrier children with low or undetectable anti-HBs. There were 214 subjects receiving booster vaccination in the first year, 49 in the second year, and 14 in the third year. We followed up all the hepatitis B markers yearly for 3 years.

Vaccination schedules: The vaccinees received a 5-μg dose of plasma-derived HB vaccine (Hevac B; Pasteur Institute, Marnes-la-Conquette, France) at 0, 1, 2 and 12 months of age. In addition, 0.5 mL (145 IU) of hepatitis B immunoglobulin was given within 24 hours after birth to those infants whose mothers had HBeAg or serum HBsAg reciprocal titers of 2560 or more. Either 20μg of Engerix B (SmithKline

Beecham Biologicals, Belgium) or 5 μg of Recombivax-B (Merck, Sharp and Dohme, West Point, PA) were given as a booster in our study.

Laboratory studies: Serum HBsAg, anti-HBs and anti-HBc were tested by radioimmunoassays using Ausria II, Ausab and Corab (Abbott Laboratories, North Chicago, IL), respectively.

Statistics: Differences in frequency between groups were examined by chi-square tests. A significant difference was considered if P was < 0.05. A P value between 0.05 and 0.1 was considered to show a trend.

Results

The serologic status:

The seroprevalence of HBsAg, anti-HBs and anti-HBc for the first year (7 years old) and three year follow-up are shown in Table 1. The overall seropositivity rate of anti-HBs (S/N $\geqq$ 2.1) was 78.1% (1044 of 1337) at age 7, but only 57.7% (772 of 1337) sustained a seroprotective level (S/N > 10). The seropositivity rate increased to 83.4% (1024 of 1228) at age 8, and decreased gradually as 78.0% (884 of 1133) at age 9, and 73.0% (775 of 1061) at age 10. The corrected seropositivity rate which excluded the boostered children was 84.2% (856 of 1017) at age 8, 79.4% (718 of 904) at age 9, and 76.2% (633 of 831) at age 10. The increased seropositivity at age of 8 years might be due to boostering and also the differences of anti-HBs seropositivity in the group who lost follow-up.

The "protective" level at the age of 8 was found only in 61.6%, but it increased to 52.0% at the age of 9, and 46.3% at the age of 10. No sexual predilection was found in the anti-HBs seropositivity in these 4 years (P=0.823, 0.247, 0.242, and 0.575, respectively). The annual disappearance rate of positive anti-HBs was followed up in the children who had positive anti-HBs at 7 years of age without further booster dose. It was calculated as the number of children who became negative anti-HBs divided by the total number of follow-up children and further divided by the years of follow up. It was averaged as 5.0%, 6.4%, and 5.5% when followed up till 8~10 years of age, respectively. Therefore, the positive anti-HBs disappeared steadily from year to year. The natural booster rate of anti-HBs was followed up in the children who had negative anti-HBs at 7 years of age without further booster dose. It was calculated as the number of children who became positive anti-HBs divided by the total number of follow-up children and further divided by the years of follow up. It was averaged as 17.1%, 12.5%, and 6.3% when followed up till 8~10 years of age, respectively. The

results indicated that the positive anti-HBs from natural booster did not sustain well and would decay by times.

HBsAg carrierate was 0.6-0.7% HBsAg carriers at age 7 to age 10. No new carrier was found in the 4 years. Including the 8 carriers, 24 children (1.8% of 1337 subjects) developed serologic evidence of natural infection with a positive anti-HBc at age 7. The anti-HBc seropositivity was 1.9% (23 of 1228) at age 8, 1.9% (22 of 1133) at age 9, and 2.0% (21 of 1061) at age 10. The new HBV infection rate (with newly developed anti-HBc seropositivity) was 0.58% (7 of 1212) at age 8, 0.5% (5 of 1116) at age 9, 0.29% (3 of 1043) at age 10.

Booster effect on non-carrier children without protective level of anti-HBs:

Among the 565 children who had a low or undetectable titer of anti-HBs (S/N <10) at age 7, nine of them were HBsAg seropositive. Excluding these carriers, 210 received booster vaccination under parental consent and 302 did not boostered but were followed (Table 2). There was no significant difference in gender (P=0.677) or baseline anti-HBc seropositivity rate (P=0.171) between the boostered and non-boostered group. An anamnestic response was defined for the children who had lost anti-HBs but developed protective anti-HBs (S/N > 10). Accordingly, 124 children (59.0% of 210) in the boostered group and 28 children (9.3% of 302) in the non-boostered group developed an anamnestic rise of anti-HBs 1 year later (P=0.000). There was no new anti-HBc-seroconversion suggesting natural infection in those who developed an anamnestic response. Among the non-carrier children with low titer of anti-HBs at age 7, the difference of anti-HBs seropositivity between boostered and non-boostered group at follow up (Table 2) was significant (P= 0.000 at age 8-10).

The annual disappearance rate of positive anti-HBs in boostered group was followed up in the children who had non-protective anti-HBs at 7 years of age,

received booster dose and developed positive anti-HBs at 8 years of age without further booster dose. It was calculated as the number of children who became negative anti-HBs divided by the total number of follow-up children and further divided by the years of follow up. It was averaged as 16.1%, and 11.1% when followed up till 9~10 years of age, respectively. The higher anti-HBs disappearance rate compared to the control group who had positive anti-HBs at age of 7 indicated that the positive anti-HBs by booster dose sustained less longer than the control group. There were still 35 non-carriers who had booster vaccination at age 7-10 but never sustained positive anti-HBs (their S/N<2.1). However, no new carrier was noted during the follow up period. There was no significant difference of anti-HBc seropositivity (Table 3) in non-carriers between the boostered and non-boostered group (P= 0.223, 0.002, 0.102, at age 8-10, respectively).

Discussion

According to the previous literatures, the level of anti-HBs does wane after vaccination, quite rapidly within the first year and more slowly thereafter.[18,19] Our community-based study also yielded the decline of the level of anti-HBs with time. The seronegativity increased from 21.9% at age of 7 to 29.5% at age of 11. However, the persistence of protection after vaccination and the cost/efficacy of reboosting policy to maintain an anti-HBs level > 10 mIU/mL are still debated.[20] Huang et al. used the IL-5 production of T cells as a marker of immunologic memory.[21] All subjects who were seronegative for anti-HBs at 10 years of age maintained their ability to respond to HBV suggests that immunologic memory induced by the HB vaccine could well last for 10 years.[21] Besides, in the endemic area such as Taiwan, frequent "natural boosts" may increase the seropositivity of anti-HBs.[22,23] The anamnestic response does exist in our study at age of 7, six years after the last dose of vaccination. Besides, the boostered group in non-carriers had a significant rise in anti-HBs seropositive rate compared to the non-boostered group. There was no new carrier in the 5 year follow-up and the difference of anti-HBc seroconversion rate was not significant between boostered and non-boostered group. Therefore, the booster vaccination seemed not necessary before 11 years of age, same as suggested in the previous literatures. [1,15,21]

Although the anamnestic response and absence of new carrier objected the booster vaccination before 11 years at our study, continuing follow-up is needed. As these children grow up to be adolescents, sexual exposure is the main route for HBV infection. Whether the anamnestic response can protect them or they get infection and become carriers is doubtable. So Zuckerman suggested a booster dose given in early adolescence, combined with a health education package.[24]

There were 35 non-carriers who never sustained the level of seropositivity

of anti-HBs (S/N>2.1) despite booster vaccination. They are referred to be nonresponders. While several factors are reported to affect adversely the antibody response to HBsAg including the site and route of injection, gender, advancing age, body mass (overweight), immunosuppression and immunodeficiency, the mechanisms underlying nonresponsiveness to the S component of HBsAg in humans remain largely unexplained, and evidence is accumulating that there is an association between different HLA-DR alleles and specific low responsiveness in different ethnic populations.[25] A high frequency of HLA class II allele DRB1*0701 and the phenotype B44; DRB1*0701; DQB1*0201 was found in nonresponders compared to controls.[25] Besides, the A1, B8, DR3, DR7, DR2[26], or B8, SC01, DR3[27], or DR14-DR52 in Taiwanese population[28] have been reported. However, there was no evidence of HBV infection in our nonresponders.

Among the 9 carriers of HBsAg, only one did not receive any vaccination. However, the other 8 children received vaccinations with 3-5 doses (2 had 3 doses, 5 had 4 doses, and 1 had 5 doses). Three of them had an HBsAg positive mother and others did not have a positive family history of HBsAg carrier. As we know, a monoclonal antibody that recognizes a region within this *a* epitope through vaccination is capable of neutralizing HBV.[24] However, significant HBV infection may occur due to exposure to an overwhelming dose of HBV, production of antibody recognizing only subtype specific determinants of HBsAg such as *d, w, y,* or *r,* instead of the *a* determinant common to all subtypes, or infection by an escape mutant of HBV producing HBsAg with a modified *a* determinant that is not effectively neutralized by anti-HBs.[12,24] Among these 9 carriers, only one had HBsAg *a* determinant variant. This girl was born to a carrier mother and received HBIG and fully vaccinated. Since Hsu *et al* reported that universal vaccination has accelerated an accumulation of HBsAg *a* determinant mutants with amino acid changes critical

for immune escape in vaccinated children became carriers, new vaccination strategies should be considered.[29]

We concluded that the seropositivity of anti-HBs after HB vaccination does wane with time at a rate of 1.3% per year but a booster dose may induce anamnestic response. However, the anti-HBc seroconversion rate does not show significant differences between boostered and control group of non-carrier children. And no new carrier was noted during the follow-up period. Therefore, the booster vaccination before 11 years for children who have received universal vaccination for HBV during infancy is not suggested.

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Table 1. The serologic status at the age of 7~10 years.

Years of age		7	8	9	10
Numbers of enrollment		1337	1228	1133	1061
HBsAg	Positive	9 (0.7%)	8 (0.7%)	8 (0.7%)	8 (0.7%)
Anti-HBs (S/N)	≧ 10	772 (57.7%)	757 (61.6%)	589 (52.0%)	491 (46.3%)
			632(62.1%)*	489(54.1%)*	411(49.5%)*
	2.1-9.9	272 (20.3%)	267 (21.7%)	295 (26.0%)	284 (26.8%)
			224(22.0%)	229(25.3%)*	222(26.7%)*
	< 2.1	293 (21.9%)	204 (16.6%)	249 (22.0%)	286 (27.0%)
			161(15.8%)*	186(20.6%)*	198(23.8%)*
Anti-HBc	Positive	17 (1.3%)	19 (1.5%)	19 (1.7%)	19 (1.9%)

The * denote the corrected seroprevalence of HBV surface antibodies (the subjects didn't receive any booster dose between age of 7-10).

Table 2. Among the non-carriers who had low titer of anti-HBs (S/N<10) at age 7, the seropositivity of anti-HBs (S/N≧2.1) in boostered and non-boostered groups.

Seropositivity of Anti-HBs	Boostered group		Non-boostered group		*P* value
	Positive	Negative	Positive	Negative	
Age of 8 years	165 (78.6%)	45 (21.4%)	155 (51.3%)	147 (48.7%)	0.000
Age of 9 years	163 (71.2%)	66 (28.8%)	91 (35.4%)	166 (64.6%)	0.000
	134* (73.6%)	48* (26.4%)	91* (35.4%)	166* (64.6%)	0.000
Age of 10 years	140 (61.4%)	88 (38.6%)	65 (28.3%)	165 (71.7%)	0.000
	120* (69.4%)	53* (30.6%)	65* (28.3%)	165 (71.7%)	0.000

The boostered group had booster dose at or after age of 7.

The * denote that the booster group had only received boostering at age of 7.

The seronegativity means S/N <2.1.

Table 3. Among the non-carriers who had low titer of anti-HBs (S/N<10) at age of 7, the seropositivity of anti-HBc in boostered and non-boostered group.

Anti-HBc	Boostered group		Non-boostered group		*P* value
	Positive	Negative	Positive	Negative	
Age of 8 years	0	209	1	297	>0.1
Age of 9 years	0	228	3	244	>0.1
Age of 10 years	0	227	2	225	>0.1

The boostered group had received boostering at or after age of 7.